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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,481	11/01/2001	Qun-Yong Zhou	P-UC 5016	4599
23601	7590	09/09/2004	EXAMINER	
CAMPBELL & FLORES LLP 4370 LA JOLLA VILLAGE DRIVE 7TH FLOOR SAN DIEGO, CA 92122			JIANG, DONG	
			ART UNIT	PAPER NUMBER
			1646	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

10/016,481

Applicant(s)

ZHOU ET AL.

Examiner

Dong Jiang

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1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 12 July 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-32,42 and 91-96 is/are pending in the application.
- 4a) Of the above claim(s) 1-32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 42 and 91-96 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 1-32,42 and 91-96 are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED OFFICE ACTION**

Applicant's amendment filed on 12 July 2004 is acknowledged and entered. Following the amendment, claims 33-41 and 43-90 are canceled, claim 42 is amended, and the new claims 91-96 are added.

Currently, claims 1-32, 42 and 91-96 are pending, and claims 42 and 91-96 are under consideration.

Note: applicants state in "Remarks" that claim 53-90 stand *withdrawn*, which is not consistent with that in the claim list, where claim 53-90 are *canceled*. Correction is required in response to this Office Action.

#### ***Restriction requirement***

Applicants maintain their traversal of the final restriction requirement. However, as the restriction requirement was deemed proper and was therefore made FINAL in the last Office Action for the reasons of record, further traversal is not timely. Applicants only recourse in this matter is to petition under 37 CFR 1.144.

#### **Withdrawal of Objections and Rejections:**

All objections and rejections of claims 33-41 and 43-52 are moot as the applicant has canceled the claims.

The rejection of claim 42 under 35 U.S.C. 102(e) as being anticipated by Sheppard et al. (US 6,485,938 B1) is withdrawn in view of applicant's amendment.

#### **Formal Matters:**

##### ***Sequence compliance***

The specification is objected to based on minor errors related to the "Sequence Listing" rules. In particular, on page 51, line 26, a 6-amino acid sequence is recited, however, the sequence identifier (SEQ ID NO:3) is missing, which is required according to MPEP, where it

states that where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing", reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application (MPEP 2422, 37 CFR 1.821 (d)).

Applicant is given the statutory time, from the mailing date of this Office Action within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

### ***Claims***

Claim 91 is objected to for encompassing a non-elected subject matter, SEQ ID NO:3. The applicant is required to amend the claims to read only upon the elected invention.

Claim 42 is objected to for the following informalities, appropriate correction is required for each item:

In line 3, "calcium ion indicator" should be "*a* calcium ion indicator".

In line 5, "a calcium ion indicator" should be "*the* calcium ion indicator".

### **Objections and Rejections under 35 U.S.C. 112:**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 42 remains rejected, and claims 91-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42 remains because it is unclear whether "a compound that mobilizes calcium ion" is an agonist or an antagonist of the receptor, since they are mutually exclusive, and only one may have the activity of mobilizing calcium ion.

Claim 92 is indefinite for the recitation of "said preparation is a cell *line*". "Said preparation is a cell" is suggested. Further, "said cell is ..." (instead of "said cell line is") is suggested for claim 93.

Claims 95 and 96 are indefinite because it is unclear how to determine which candidate compound is an agonist or an antagonist of the receptor as the independent claim 42 does not indicate "a compound that mobilizes calcium ion" is an agonist or an antagonist of the prokineticin receptor (simply a "ligand").

The remaining claims are rejected for depending from an indefinite claim.

**Rejections Over Prior Art:**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 42, 91, 92, and 94-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sheppard et al. (US 6,485,938 B1), in view of Costanzo (Physiology, Board Review Series, page 21, Williams & Wilkins, 1995).

The teachings of Sheppard and Costanzo are reviewed in the last Office Action. Briefly, Sheppard teaches a human protein, Zven1 receptor, having an amino acid sequence of SEQ ID NO:2, which is 100% identical to SEQ ID NO:6 of the present invention, and a method of

identifying a Zven agonist or antagonist as that a Zven agonist binds with a Zven receptor and stimulates a response by a cell expressing a Zven receptor, and a Zven antagonist that may diminish Zven agonist activity by a competitive or non-competitive binding of the antagonist to the Zven receptor (column 41, lines 5-17), and indicates that Zven, the agonists and the antagonists thereof are valuable in both in vivo and in vitro uses (column 41, lines 40-41), such as in the treatment of diarrhea and Crohn's disease (column 55, the third paragraph), and inhibiting contraction of the ileum (column 41, lines 55-59). Additionally, Sheppard teaches that metabolic events that are often linked to receptor-ligand interaction include ..., mobilization of cellular calcium, ... (column 10, lines 58-61); and that the activity of a Zven agonist or antagonist can be determined by assays well known in the art (references provided), such as ... changes in ion channel influx, ... (column 41, the last paragraph to column 42, the first paragraph). Sheppard does not explicitly teach a method of identifying a prokineticin receptor ligand by measuring a calcium ion indicator signal or the mobilization of calcium ion (as the present claims). Costanzo teaches steps in excitation-contraction coupling in smooth muscle, including an increase in intracellular calcium levels (page 21, "B").

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to identify a Zven (prokineticin) receptor ligand by using a cell expressing Zven receptor as taught by Sheppard, and monitoring the effect of the ligand on calcium mobilization because metabolic events that are often linked to receptor-ligand interaction include mobilization of cellular calcium following the method taught by Costanzo, and by determining the ability of a ligand to modulate smooth muscle contraction because Zven is involved in contractility of tissues, such as gastrointestinal tissues (smooth muscle contraction) as taught by Sheppard, and because smooth muscle contraction involves calcium mobilization as taught by Costanzo. The person of ordinary skill in the art would have been motivated to identify a prokineticin receptor agonist or antagonist because they are valuable in both in vivo and in vitro uses including therapeutic applications as taught by Sheppard, and reasonably would have expected success because the assays for measuring calcium mobilization have been well-established in the art, and are widely practiced in the field.

At page 12 of the response filed on 12 July 2004, applicants argue (in advance) that Sheppard and Costanzo references would not apply to the newly amended claim 42 and the newly added claims 91-96. Applicants argument has been fully considered, but is not deemed persuasive for reasons below.

At page 12 of the response, the applicant argues that Sheppard fails to teach that Zven-Zven receptor binding causes mobilization of  $\text{Ca}^{2+}$ , rather Sheppard provides a laundry list of metabolic events that are often linked to receptor-ligand interactions including mobilization of cellular calcium, and that at best Sheppard indicates that calcium ion mobilization is one possible metabolic event that might arise from Zven binding to a Zven receptor. Applicants further argue, at page 13 of the response, that Costanzo does not provide the missing teaching of detecting a calcium indicator signal to identify a prokineticin receptor ligand, that at best Costanzo teaches that depolarization of smooth muscle cells membrane opens  $\text{Ca}^{2+}$  channel, but does not teach that Zven-Zven receptor binding causes depolarization of smooth muscle cell membrane. Applicants further argue that a person of ordinary skill in the art would have been just as likely to be led by Sheppard to look for potassium or chloride ion channel activity, or other metabolic activity as a consequence of Zven-Zven receptor binding, and that neither reference nor in combination could have led the claimed method with a reasonable expectation of success. These arguments are not persuasive for the following reasons:

In addition to what are *often* being tested in the "laundry list" (merely a few events) such as mobilization of cellular calcium, Sheppard specifically teaches the involvement of Zven in smooth muscle contractility of contractile tissues such as gastrointestinal tissues (column 42, the second paragraph), and that, as an illustration, Zven antagonists can be used to inhibit contraction of the ileum (column 41, lines 57-58). Further, it is well established and evidenced by the Costanzo reference that the excitation-contraction coupling in smooth muscle is associated with an increase in intracellular calcium levels. Therefore, it is instantly obvious to a person of ordinary skill in the art, as a priority, to test mobilization of cellular calcium by Zven-Zven receptor binding based on the combination teachings by Sheppard and Costanzo regardless whether Costanzo teaches the mechanism of depolarization of smooth muscle cell membrane by Zven-Zven receptor binding, and reasonably to have expected success because of the

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involvement of Zven in smooth muscle contractility; the well established association between smooth muscle contractility and an increase in intracellular calcium levels; and that the assays for measuring calcium mobilization have been well-established in the art, and are widely practiced in the field.

**Conclusion:**

No claim is allowed.



**Advisory Information:**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

  
**JANET ANDRES**  
**PRIMARY EXAMINER**

Dong Jiang, Ph.D.  
Patent Examiner  
AU1646  
8/30/04